PATENT

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Bethany Crandell — Bethany Crandell

7 April, 2010 — Date of Deposit

Applicant: Markou et al.	Art Unit: 1627
Serial No.: 10/527,525	Examiner: Kendra Carter
I.A. Filing Date: Sep. 10, 2003	Confirmation No.: 3218
Title: METHODS FOR TREATING DISORDERS ASSOCIATED WITH mGLU RECEPTORS INCLUDING ADDICTION AND DEPRESSION	Our Ref.: TSRI 897.1

APPEAL BRIEF

MAIL STOP: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants appeal the Final Office Action, dated December 15, 2009 ("Office Action," attached as Ref. 17), and the rejection of claims 1-3, 6, 7, 9, 16, 27, 28 and 32 in the above-referenced patent application.

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I. Real Party in Interest

The present application has been assigned by the inventors to The Scripps Research Institute, which is the real party in interest.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of Claims

Claims 1-3, 6-7, 9-10, 14-17, 19, 27-28 and 32 are pending.

Claims 4, 5, 8, 11-13, 18, 20-26, 29-31, and 33 were canceled by Applicants

Claims 10, 14, 15, 17 and 19 are withdrawn from consideration by the Examiner

Claims 1-3, 6, 7, 9, 16, 27, 28 and 32 are rejected.

Claims 1-3, 6, 7, 9, 27, 28 and 32 are on appeal.

IV. Status of Amendments

All amendments previously submitted by Appellants have been entered.

No amendment was filed by Appellants subsequent to the noted Office Action.

V. Summary of Claimed Subject Matter

The claimed inventions relate to treatment of drug dependence/addictions and withdrawal symptoms associated therewith. Specifically, Independent claim 1 is directed to a method of treating drug dependence, such as nicotine addiction, alcohol addiction, opiate addiction and cocaine addiction. The method entails the administration to a subject in need of treatment (1) a first antagonist for metabotropic glutamate receptor 2 (mGluR 2) and/or metabotropic glutamate receptor 3 (mGluR 3) and (2) a second antagonist for metabotropic glutamate receptor 5 (mGluR 5). Claim 2 more specifically recites administration of a combination of a mGluR2 antagonist and a mGluR5 antagonist, while claim 3 specifies the combination of a mGluR3 antagonist and a mGluR5 antagonist. Claims 6, 7, and 9 depend from claim 1. Support for these claims is provided in the claims as originally filed and in the specification, e.g., at page 2, last paragraph to page 3, 4th paragraph; page 11, first two paragraphs; page 17, last paragraph to page 19, penultimate paragraph; and Example 3 at pages 64-79 (especially disclosures related to Experiment 3.5 at page 73, 1st paragraph; page 76, last paragraph; and page 79, first two paragraphs).

Claim 16 is directed to treating addictive disorders via the use of a combination that comprises a first active ingredient which is a mGluR2 antagonist or a mGluR3 antagonist and a second active ingredient which is a mGluR5 antagonist. Support for this claim is provided in the specification, e.g., at page 11, last paragraph to page 12, penultimate paragraph; and claim 16 as originally filed.

Similar to claims 1-3, independent claim 27 is also directed to treating addictive disorders including nicotine addiction and alcohol addiction. However, this claim specifies administration of a mGluR5 antagonist during a first time period and administration of a mGluR2 or mGluR3 antagonist during a second time period. Support for this claim is provided in the specification, e.g., page 23, last paragraph to page 14, second paragraph; and original claims 27-28 as filed.

VI. Grounds of rejection to be reviewed on appeal

Issue 1. Whether Claims 1-3, 6, 7 and 16 are unpatentable under 35 U.S.C. § 103(a) over Adam et al. (U.S. Patent No. 6,406,094; attached as Ref. 1) in view of Corsi et al. (U.S. Application 2003/0195139; attached as Ref. 2) or Chiamulera et al. (Nat. Neurosci. 4:873-874, 2001; attached as Ref. 3)?

Issue 2. Whether Claims 9, 27, 28 and 32 are unpatentable under 35 U.S.C. § 103(a) over Chiamulera et al. in view of Adam et al.?

VII. Argument

The Examiner rejected claims 1-3, 6, 7 and 16 under 35 U.S.C. § 103(a) as allegedly unpatentable over Adam et al. (U.S. Patent No. 6,406,094) in view of Corsi et al. (U.S. Application 2003/0195139) or Chiamulera et al. (Nat. Neurosci. 4:873-874, 2001). The Examiner additionally rejected claims 9, 27, 28 and 32 under 35 U.S.C. § 103(a) as allegedly unpatentable over Chiamulera et al. in view of Adam et al. and some other art cited in the subject specification. The rationale underlying the Examiner's the rejection of claims 1-3, 6, 7 and 16 can be summarized as follows.

(1) "Adam et al. teaches compounds that act as Group II (i.e., mGluR2 and 3) metabotropic glutamate receptor antagonist (see column 16, lines 47 and 48) and treat conditions such as nicotine addiction, and opiate addiction (see column 1, lines 54-56 and column 3, lines 20-24; . . ." (Office Action, paragraph bridging page 3 and page 4; emphasis added);

(2) Corsi et al. teaches treating substance dependence with an mGluR5 antagonist; and Chiamulera et al. teaches administration of a mGluR5 antagonist to decrease cocaine self-administration (Office Action, page 4, paragraphs 3 and 4);

(3) Because Adam et al. and Corsi et al. (or Chiamulera et al.) both teach methods for treating addictive disorders, the skilled artisan would be motivated to combine the methods taught in the cited art, i.e., using both an antagonist for mGluR2 or mGluR3 and an antagonist for mGluR5 in treating addictive disorders (Office Action, paragraph bridging page 4 and page 5).

The Examiner's rationale for rejecting claims 9, 27, 28 and 32 is based on assertions similar to that noted above, except for reference to some additional art for the

teaching of certain claim limitations present in these claims which are not disclosed in the primary references, i.e., Adam et al. and Chiamulera et al. Accordingly, unless otherwise noted, Appellants' arguments presented herein are intended to address both rejections (Issue 1 and Issue 2 set forth above).

As explained in detail below, Appellants respectfully traverse these rejections because no prima facie case of obviousness can be established on the evidence and reasoning provided by the Examiner. In brief, the prior art does not teach each and every element of the claimed inventions. In addition, the Examiner did not provide a sufficient reason or explicit analysis of why the skilled artisan would combine elements recited in the claimed inventions. Instead, teachings of the prior art, including references cited by the Examiner, would actually teach away from the claimed inventions. Furthermore, Appellants' inventions have demonstrated surprising results that would not have been expected from the prior art.

1. *The prior art did not teach every element of the claimed inventions*

It is well established that, to sustain an obviousness rejection, it is necessary to show "that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." See, e.g., *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007). See also, MPEP §§ 706.02(j) and 2143. In the instant case, as elaborated in the following sections, the prior art did not teach all the elements recited in the claimed inventions. This is because, the prior art, including Adam et al. (one of the primary references relied on by the Examiner), did not teach treating addictive disorders with antagonist compounds for mGluR2 or mGluR3 as alleged by the Examiner. Rather, prior to the claimed inventions, it was not known in the art that antagonizing Group II glutamate receptors (i.e., mGluR2 or mGluR3) will be conducive to treating disorders mediated by metabotropic glutamate receptors. To the

contrary, the consensus review in the relevant scientific fields was that agonizing (not antagonizing) mGluR2 and mGlu3 is beneficial for treating drug dependence. On the other hand, Adam et al., which was the sole reference cited by the Examiner for the alleged teaching of treating addictive disorders with mGluR2/3 antagonists, merely alluded to possible therapeutic uses of certain antagonist compounds for mGluR2 and mGluR3. There was no actual data or other substantiation in Adam et al. to support the assertion.

A. **Prior art teaching of mGluR2/3 agonism for treating addictions**

The present inventors were the first to experimentally demonstrate that mGluR2/3 antagonists are effective in the treatment of drug dependence and withdrawal symptoms. The inventors' study was described in detail in Example 1 of the subject specification and also in a corresponding post-filing publication, Kenny et al., (J. Pharmacol. Exp. Ther. 306:1068-76, 2003; attached as Ref. 16). Prior to the claimed inventions, the consensus view in the scientific community on the connection between modulating mGluR2/3 receptors and reducing withdrawal symptoms was the opposite to that reflected by the results obtained by the present inventors. At that time, several research groups have shown that agonists (not antagonists) of mGluR2/3 were able to attenuate withdrawal symptoms and to treat morphine or nicotine dependence. The apparent difference between the prior art studies and the subject disclosure is explained in the specification, e.g., at page 43, middle paragraph; and page 45, 3rd paragraph to page 46, 1st paragraph.

Specifically, Helton et al. (Neuropharmacol. 36:1522-6, 1997; attached as Ref. 13) reported that the mGluR2/3 agonist LY354740, when administered to nicotine dependent rats, resulted in a dose-dependent attenuation of the enhanced auditory startle response following withdrawal from chronic nicotine exposure. Helton et al. further noted that their data indicate that the mGluR2/3 agonist could be effective in treating nicotine withdrawal symptoms during smoking cessation in humans. Similar

data suggesting the use of mGluR2/3 agonists in treating withdrawal symptoms were also reported in other scientific papers published prior to Appellants' inventions. For example, Vandergriff and Rasmussen (Neuropharmacol. 38:217-22, 1999; attached as Ref. 14) reported that the mGluR2/3 agonist LY354740 was able to reduce symptoms in morphine dependent rats following withdrawal from chronic morphine exposure, and suggested its potential therapeutic use in treating human opiate dependence. In another study, Fundytus and Coderre (Brit. J. Pharmacol. 121:511-4, 1997; attached as Ref. 15) reported that the mGLuR2/3 agonist DCG-IV was able to significantly attenuate withdrawal symptoms in morphine dependent rats. The authors suggested that activation of the mGluR receptors could reduce withdrawal symptoms in human patients.

Thus, it is readily apparent that, prior to the claimed inventions, scientific publications in the prior art taught that activation of mGluR2/3 receptors could produce beneficial effects in treating drug dependence (e.g., reducing withdrawal symptoms). By extension, one would understand that inhibition of mGluR2/3 receptors (e.g., via an antagonist compound) is likely to exacerbate withdrawal symptoms (or at best, to have no effect in ameliorating withdrawal symptoms). One would certainly not be motivated by the unsubstantiated speculation in Adam et al., as discussed below, to attempt treatment of drug dependence with an mGluR2/3 antagonist. To the contrary, the consensus view of the leading scientists in the relevant technical fields (as evidenced by the above-noted publications) would undoubtedly have led a skilled artisan away from such a treatment.

B. Disclosure of Adam et al.

The Examiner relied on Adam et al. for the alleged art teaching of the use of mGluR2/3 antagonists in treating addictive disorders. However, the Examiner's reliance on Adam et al. in rendering and maintaining the obviousness rejection of the claimed inventions in clearly unjustified. This is because Adam et al. did not actually

teach the use of mGluR2/3 antagonism for treating addictions. Instead, Adam et al. disclosed certain compounds which are purportedly Group II mGlu receptor antagonists. Adam et al. additionally speculated about possible use of the compounds in the treatment of a variety of diseases or conditions, including addictive disorders. The relevant descriptions in Adam et al., including the excerpts cited by the Examiner in rejecting the claimed invention in the Office Action, are reproduced below:

> "These compounds have been discovered to act as metabotropic glutamate receptor antagonists and accordingly are useful for the treatment of a range of neurological disorders, including psychosis, schizophrenia, Alzheimer's and other cognitive and memory disorders." [Adam et al., Col. 1, lines 54-58]
>
> "Further treatable indications are . . . as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depressions." [Adam et al., Col. 3, lines 16-24]

Other than these naked assertions, there were neither experimental data nor plausible substantiation anywhere in Adam et al. to prove or suggest that the compounds are indeed effective in treating drug dependence. More importantly, the pure speculation of Adam et al. is contradictory to the above-discussed results from actual scientific studies that were published in peer reviewed journals. Based on the speculative nature of the relevant assertions in Adam et al., as well as their contradiction to the consensus view of the skilled artisans in the relevant art, it is an inescapable conclusion that the prior art, including Adam et al., did not teach in any enabling manner treatment of drug dependence via mGluR2/3 antagonism.

C. **Examiner's assertion of presumption of validity of Adam et al.**

Appellants have previously pointed out that Adam et al., due to its absence of actual data or plausible substantiation, is not enabling with respect to the alleged

teaching of treating addictions via mGluR2/3 antagonism. In the Office Action, the Examiner dismissed Appellants' notion and asserted that "Adam et al. is a US Patent, which is believed to be enabled by its disclosure; . . . " (Office Action, page 8, last paragraph). With due respect, Appellants note that the Examiner's position is undoubtedly incorrect. This is because the presumption of validity of an issued U.S. patent only applies to the claimed invention (i.e., the claims) in the patent. The presumption certainly does not apply to any statement in the patent specification. It can by no means be applied to any unsubstantiated assertions or pure speculations imbedded in a patent specification, let alone speculations that are clearly contradictory to the consensus view of the skilled artisans that was founded on experimental results published in peer-reviewed scientific literatures.

From the foregoing, it can be concluded that the prior art did not teach treatment of drug dependence by antagonizing mGluR2 or mGluR3. Since the cited art did not teach each and every element of the presently appealed claims, a prima facie case of obviousness could not be established.

2. *No rationale for combining mGluR2/3 antagonism and mGluR5 antagonism*

Even assuming for the sake of argument that the prior art references cited by the Examiner did separately teach all the claimed elements, the rejected inventions are nonetheless non-obvious because no sound reasoning or rationale can be drawn from the prior art to combine the claimed elements. As noted by the Supreme Court, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *KSR, KSR, 550 U.S. at ___, 82 USPQ2d at 1391.* The Board of Patent Appeals and

Interferences has also emphasized that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" (*In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) cited with approval in KSR) (emphasis added).

In the present case, the obviousness rejections rendered by the Examiner are improper because the Examiner did not provide any articulated reasoning or rationale for combining mGluR2/3 antagonism and mGluR5 antagonism in the treatment of addictions. In alleging that one would be motivated to combine a mGluR2/3 antagonist and a mGluR5 antagonist, the only reason advanced by the Examiner is that "they both treat addictive disorders" (Office Action, page 5, first paragraph). Other than this conclusory statement, the Examiner did not otherwise provide any scientific evidence or sound rationale to support the conclusion. More importantly, the Examiner's conclusion was also made in disregard to the fact that the relevant teachings available in the prior art all suggest that one would likely be taught away from such a combination.

A. **Counter-intuitive to target both mGluR2/3 and mGluR5**

It would have been counterintuitive to antagonize both a Group I mGluR (e.g., mGluR5) and a Group II mGluR (i.e., mGluR2 or mGluR3) in the treatment of addictions. This is because Group I glutamate receptors, such as mGlu5, are located postsynaptically and are excitatory receptors; thus, blockade of these receptors results in decreased glutamate signaling. On the other hand, Group II receptors, such as mGluR2/3, are located presynaptically and are inhibitory receptors; thus, their blockade will lead to increased release of glutamate and thus increased glutamate signaling. Such different biological activities of mGluR2/3 and mGluR5 were well known in the art, as evidenced by some of the pre-priority publications on record including, e.g., Kilbride et al., Eur. J. Pharmacol. 356:149, 1998 (attached as Ref. 5); Vignes et al.,

Neuropharmacol. 34:973-82, 1995 (attached as Ref. 6); and Schoepp, Neurochem. Int., 24:439, 1994 (attached as Ref. 7). The counter-intuitive nature of combining mGluR2/3 antagonism and mGluR5 antagonism due to the different activities of the receptors is explained in the attached copy of a declaration of Dr. Athina Markou under 37 CFR § 1.131 (attached as Ref. 8). The declaration was previously submitted by Appellants in the subject application. Dr. Athina Markou, a co-inventor of the claimed inventions, is an expert in the field of neuropharmacology and substance addictions. Dr. Markou stated in the declaration that "references from the literature suggesting that one should expect opposite neurochemical and behavioral effects of metabotropic glutamate 2/3 receptor (GluR2/3) antagonists and metabotropic glutamate receptor 5 (mGluR5) antagonists." The references referred to by Dr. Markou in the declaration include publications published before or around the same time of the priority date of the claimed inventions, e.g., Mills et al. (J. Neurochem. 79: 835-48, 2001; attached as Ref. 9), Xi et al. (J. Pharmacol. Exp. Ther. 300:162-71, 2002; attached as Ref. 10), Thomas et al. (Neuropharmacology 41: 523-7 2001; attached as Ref. 11) and de Novellis et al. (Eur. J. Pharmacol. 462: 73-81 2003; attached as Ref. 12).

The counter-intuitive nature to co-antagonize both Group I and Group II mGlu receptors suggest that a skilled artisan would not choose to combine the elements recited in the Appellants' claims. To the contrary, the artisan would probably be concerned that, due to the localization of these receptors in the synapse and their apparent opposing effects on postsynaptic glutamate signaling, co-administration of mGluR2/3 and mGluR5 antagonists would likely antagonize each other's activity to the extent that their effects are neutralized.

B. **The art taught away from co-antagonizing mGluR2/3 and mGluR5**

Citing Fundytus et al. (Brit. J. Pharmacol. 120:1015-20, 1997; attached as Ref. 4), the Examiner has previously rejected the claimed inventions as allegedly anticipated. The Examiner asserted that Fundytus et al. discloses treatment of morphine withdrawal

symptoms with α-methyl-4-carboxyphenylglycine (MCPG). The Examiner also noted that MCPG is an antagonist of both Group I glutamate receptors and Group II glutamate receptors. Appellants acknowledge that MCPG is a non-selective or dual antagonist of Group I and Group II mGluRs. However, the Examiner's interpretation of Fundytus et al. with respect to its relevance to the claimed inventions is clearly incorrect. As reiterated below, contrary to the Examiner's assertions, Fundytus et al. did not teach treatment of morphine withdrawal symptoms with MCPG. Instead, the experimental data reported in Fundytus et al. would likely teach away from Appellants' claimed inventions.

It is well known in the art that substance use/abuse and substance dependence are related but different concepts. Continued substance abuse can often lead to development of substance dependence (or addiction). Upon cessation of substance use (i.e., withdrawal), subjects already suffering from substance dependence will usually develop withdrawal symptoms. The difference between development of addiction in non-addictive subjects and withdrawal symptoms in addictive subjects is also clarified in Dr. Markou's declaration. Consistently, Appellants' claimed inventions relate to methods for treating addictive disorders in subjects that have already developed dependence on a given controlled substance (i.e., addiction). The inventions are directed to reducing, alleviating or eliminating withdrawal symptoms associated with cessation of substance use in subjects that have an existing addictive disorder. The claimed inventions are <u>not</u> directed to preventing the development of substance dependence in normal and healthy subjects who start using drugs but are not already suffering from substance dependence.

On the other hand, Fundytus et al. only showed that MCPG prevented <u>development</u> of drug dependence. Importantly, although the title and the abstract of Fundytus et al. might suggest otherwise, Fundytus et al. additionally reported that MCPG has <u>no</u> effect in the treatment of withdrawal symptoms in subjects which have already developed drug dependence. Specifically, Figure 1 of Fundytus et al., which

was relied on by the Examiner for the alleged teaching of treating drug dependence with MPCG, actually relates to a study of assessing the effect of various mGluR antagonists in the development of morphine dependence. The data were obtained from normal rats which were chronically administered morphine and at the same time treated with the mGluR antagonists. The goal of the study is clearly described in Fundytus et al., at page 1016, right column, last paragraph:

> Figure 1 illustrates the severity of abstinence symptoms during the 40 min withdrawal period in rats chronically infused with s.c. morphine and either vehicle, MCPG, MCCG or MAP4 i.c.v. This experiment was performed to determine if chronic blockade of mGluRs would attenuate the development of morphine dependence. [Emphasis added]

Results of the study is summarized in the below quoted passage of Fundytus et al. (at page 1016, left column, first paragraph, last 5 lines):

> In the present study, we showed that chronic non-selective antagonism of mGluRs with MCPG, and chronic selective antagonism of either group II or III mGluRs significantly attenuates the development of morphine dependence. [Emphasis added]

The results indicated that treatment with MCPG prevented the development of morphine dependence in normal, non-dependent rats. The lack of morphine dependence in the rats is evidenced by fewer signs of withdrawal when infusion of opiate is stopped. Unlike what the Examiner assumed, the data of Figure 1 did not show treatment of morphine dependent rats with MCPG, e.g., administration of MCPG to rats already having morphine dependence did not reduce symptoms upon opiate withdrawal.

More importantly, Fundytus et al. additionally examined whether, once rats were allowed to develop morphine dependence (i.e., "dependent rats" as noted in Fundytus et al.) and then opiate withdrawal symptoms expressed upon cessation of chronic

morphine administration, treatments with the same mGluR antagonists would have any effect on withdrawal symptoms. As indicated in Fundytus et al., the study was designed to "determine if acute blockade of mGluRs would decrease the expression of withdrawal symptoms once dependence had developed" (page 1017, left column, second to the last paragraph; emphasis added). Results from the study are shown in Figure 2 in Fundytus et al. As shown in the figure, none of the treatments (including treatment with MCPG) had any effect on withdrawal symptoms in morphine-dependent rats. Fundytus et al. expressly note that there is **"no difference between vehicle-treated rats and mGluR antagonist-treated rats"** (page 1018, left column, 2nd and 3rd paragraphs).

From the above clarifications, it is clear that Figure 1 of Fundytus et al. relates to normal rats (i.e., rats with no drug dependence) which were administered with MCPG together with morphine (to assess development of morphine dependence). The results indicate that simultaneous and chronic administration of morphine and the non-selective mGluR antagonist MCPG to healthy rats prevented the development of morphine dependence in the rats. However, the preventive effects in normal subjects evidenced by Figure 1 of Fundytus et al. are simply irrelevant to the claimed inventions. This is because the claimed inventions are not concerned with development of drug dependence, but are instead aimed at obtaining therapeutic effect in subjects who are already drug dependent. With a purpose of treating drug dependence in addictive subjects as presently claimed, the subjects certainly do not receive their medication together with the very drug on which they are already dependent (e.g., nicotine, cocaine or morphine) as in Figure 1 of Fundytus et al. Rather, the drug dependent subjects are administered only with the medication (i.e., the combination of an mGluR2/3 antagonist and an mGluR5 antagonist).

To summarize, Fundytus et al. taught that the dual mGluR antagonist MCPG PREVENTED the development of drug dependence (if co-administered TOGETHER with morphine) and the expression of the withdrawal signs in normal subjects (Fig. 1).

However, once dependence has already developed, the drug did NOT TREAT the withdrawal symptoms in the drug dependent subjects (Fig. 2). In other words, the data in Fundytus et al. that were relied on by the Examiner (i.e., Figure 1) are irrelevant to the claimed inventions. On the other hand and importantly, disclosures in Fundytus et al. that might be relevant to the claimed inventions (i.e., Figure 2) showed negative results, i.e., teaching away from the claimed invention.

3. *Surprising or unexpected results of the claimed inventions*

In addition to the prior art's lack of teaching of all the elements of the claimed inventions and also the prior art's likely teaching away from combining the recited elements, the non-obviousness nature of the claimed inventions is further demonstrated by the surprising or unexpected results disclosed in Appellants' application. For example, the subject specification disclosed that antagonizing mGluR2/3 (alone or in combination with mGluR5 antagonism) can produce beneficial effects in attenuating withdrawal symptoms (see, e.g., the summary at page 10 and Examples 3 at pages 64-79). These findings certainly represent surprising results that would not be expected from the prior art which reported that agonizing mGluR2/3 resulted in a reduction of withdrawal symptoms. Specifically, while the prior art showed that dual mGluR2/3 and mGluR5 antagonist MCPG had no effect in treating withdrawal symptoms in morphine-dependent rats, the subject specification taught that the combination of a mGluR5 antagonist (MPEP) and a mGluR2/3 antagonist (LY341495) was useful to treat established cocaine/nicotine dependence (see, e.g., Figures 14-16 and the discussions of Example 3.5 at page 76). Of particular importance is the finding by Appellants that the effect of the mGluR2/3 antagonist LY341495 on established nicotine dependence can be potentiated by co-administration of mGluR5 antagonist MPEP at a concentration where MPEP itself had no effect in treating addiction. Specifically, Figure 9C in the subject specification showed that MPEP at a dosage of 1 mg/kg had no effect in reducing nicotine or cocaine self-administration in dependent rats.

In contrast, as shown in Figures 14-15, such a MPEP dosage was effective in potentiating the inhibitory effects of the mGluR2/3 antagonist LY341495 on nicotine self-administration. The additive effects on inhibiting drug-taking behavior as illustrated by these data demonstrate that the combination of a mGluR2/3 antagonist and a mGluR5 antagonist as presently claimed is more effective than each of the two compounds alone in treating addictive disorders.

VIII. Summary of Arguments

To summarize, the presently appealed claims are non-obvious because the prior art did not teach each and every element recited in Appellants' claims. In addition, knowledge well known to the skilled artisans prior to Appellants' application would suggest that it is undesirable to combine the elements of Appellants' claims. Further, a reference cited by the Examiner as allegedly teaching Appellants' claimed inventions, i.e., Fundytus et al., could have actually led a skilled artisan away from the inventions. Moreover, the advantageous and surprising results demonstrated by the present inventors provide additional evidence that the presently claimed methods could not have been obvious. With due respect, Appellants note that the instant rejections are typical examples of "hindsight-based obviousness analysis." The alleged obviousness stems from nothing but the prohibited hindsight gleaned from Appellants' disclosure.

For all these reasons and the reasons already on record, Appellant respectfully requests that the Board of Patent Appeals and Interferences reverses the Examiner's rejections under 35 U.S.C. § 103(a) with respect to claims 1-3, 6, 7, 9, 16, 27, 28 and 32, and remands this application back to the Examiner for further examination.

If there are any fees associated with this Appeal Brief, please charge our Deposit Account No. 19-0962.

Respectfully submitted,

April 7, 2010

Date

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Claims Appendix

1. (previously presented) A method for treating drug dependence in a subject, comprising administering to a subject with drug dependence an effective amount of (a) a first antagonist which modulates metabotropic glutamate receptor 2 and/or metabotropic glutamate receptor 3, and (b) a second antagonist which modulates metabotropic glutamate receptor 5, thereby treating the disorder; wherein the drug dependence is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

2. (previously presented) A method for treating drug dependence in a subject, comprising administering to a subject with drug dependence an effective amount of (a) a first antagonist which modulates metabotropic glutamate receptor 2, and (b) a second antagonist which modulates metabotropic glutamate receptor 5, thereby treating the disorder; wherein the drug dependence is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

3. (previously presented) A method for treating drug dependence in a subject, comprising administering to a subject with drug dependence an effective amount (a) a

first antagonist which modulates metabotropic glutamate receptor 3 and (b) a second antagonist which modulates metabotropic glutamate receptor 5, thereby treating the disorder; wherein the drug dependence is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

4-5. (canceled)

6. (previously presented) The method of claim 1, wherein the drug dependence is nicotine addiction.

7. (previously presented) The method of claim 1, wherein the drug dependence is cocaine addiction.

8. (canceled)

9. (previously presented) The method according to claim 1, wherein the antagonist which modulates metabotropic glutamate receptor 5 is 2-methyl-6-(phenylethynyl)-pyridine, and the antagonist which modulates metabotropic glutamate receptor 2 and/or metabotropic glutamate receptor 3 is 2S-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propionic acid .

10. (withdrawn) A combination comprising (a) at least a first active ingredient selected from a metabotropic glutamate receptor 2 antagonist and a metabotropic glutamate receptor 3 antagonist, and (b) at least a second active ingredient being a metabotropic glutamate receptor 5 antagonist, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

11-13. (canceled)

14. (withdrawn) The combination according to claim 10 which is a combined preparation or a pharmaceutical composition.

15. (withdrawn) The combination according to claim 10 for simultaneous, separate or sequential use in the treatment of an addictive disorder or depression.

16. (previously presented) A method of treating a warm-blooded animal having an addictive disorder comprising administering to the animal a combination according to claim 10 in a quantity which is jointly therapeutically effective against an addictive disorder and in which the compounds can also be present in the form of their

pharmaceutically acceptable salts; wherein the addictive disorder is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

17. (withdrawn) A pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against an addictive disorder or depression, of a pharmaceutical combination according to claim 10 and at least one pharmaceutically acceptable carrier.

18. (canceled)

19. (withdrawn) A commercial package comprising a combination according to claim 10 together with instructions for simultaneous, separate or sequential use thereof in the treatment of an addictive disorder.

20-26. (canceled)

27. (previously presented) A method for treating an addictive disorder, comprising: a) administering to a subject in need thereof, an effective amount of a first antagonist that modulates mGluR5 during a first time period, wherein the first time period is a time period wherein the subject expects to be in an environment wherein, or exposed to

stimuli in the presence of which, the subject habitually uses an addictive substance; and b) administering a second antagonist that modulates mGluR2 and/or 3 during a second time period, wherein the second time period is a time period wherein the subject is suffering from withdrawal; wherein the addictive disorder is selected from the group consisting of nicotine addiction, alcohol addiction, opiate addiction, amphetamine addiction, cocaine addiction, and methamphetamine addiction.

28. (previously presented) The method of claim 27, wherein the antagonist that modulates mGluR5 is 2-methyl-6-(phenylethynyl)-pyridine and the antagonist that modulates mGluR2 and/or 3 is 2S-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propionic acid.

29-31. (canceled)

32. (previously presented) The method of claim 1, wherein the first antagonist and the second antagonist are administered to the subject sequentially or simultaneously.

33. (canceled)

Evidence Appendix

Copies of documents relied upon by Appellants are enclosed herewith. Dates of entry of these references into record are listed below.

I. Documents cited by the Examiner in the Office Action dated May 3, 2007

1. Adam et al. (U.S. Patent No. 6,406,094);
2. Corsi et al. (U.S. Application 2003/0195139);
3. Chiamulera et al. (Nat Neurosci. 4:873-874, 2001); and
4. Fundytus et al. (Brit. J. Pharmacol. 120:1015-20, 1997).

II. Documents submitted by Appellants on September 4, 2007 and acknowledged by the Examiner in the Office Action dated November 13, 2007.

5. Kilbride et al. (Eur. J. Pharmacol. 356:149, 1998);
6. Vignes et al. (Neuropharmacol. 34:973-82, 1995); and
7. Schoepp (Neurochem. Int., 24:439, 1994).

III. Documents submitted by Appellants on September 23, 2008 and acknowledged by the Examiner in the Office Action dated January 8, 2009

8. Declaration of Dr. Athina Markou under 37 CFR § 1.131;
9. Mills et al. (J. Neurochem. 79: 835-48, 2001);
10. Xi et al. (J. Pharmacol. Exp. Ther. 300:162-71, 2002); and
11. Thomas et al. (Neuropharmacology 41: 523-7 2001).
12. de Novellis et al. (Eur J Pharmacol 462: 73-81 2003):

IV. Documents submitted by Appellants on August 27, 2009 and acknowledged by the Examiner in the Office Action dated December 15, 2009

13. Helton et al. (Neuropharmacol. 36:1522-6, 1997);
14. Vandergriff and Rasmussen (Neuropharmacol. 38:217-22, 1999);
15. Fundytus and Coderre (Brit. J. Pharmacol. 121:511-4, 1997); and
16. Kenny et al. (J. Pharmacol. Exp. Ther. 306:1068-76, 2003).

V. 17. Final Office Action dated 12/15/2009

Related Proceedings Appendix

None.